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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,637	11/25/1997	ELAZAR RABBANI	ENZ-53(DIV5)	4643

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/978,637	RABBANI ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *318-323* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *245,247-260,262-265,268,270-274,278-280,282-284,286-290,292,296-313 and 317* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 245,247-260,262-265,268,270-274,278-280,282-284,286-290,292,296-313 and 317-323.

DETAILED ACTION

Status of Application/Amendment/Claims

1. Applicant's response filed November 6, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed May 1, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

3. Newly submitted claims 318-323 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the newly introduced claims recite two methods that have not been examined per se, and are considered distinct as follows. The two new methods are drawn to a process of introducing nucleic acid products of claims 245 or 299 into a cell, and are thus related to the products of claims 245 and 299 as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product can be used in a materially different process of using the product nucleic acid constructs of claims 245 and 299. For example, said products can be used to cleave targets in a cell free assay to determine binding and cleavage rates.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 318 to 323 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

4. Claims 245, 247-260, 262-265, 268, 270-274, 279, 280, 282-284, 286-290, 292, 296-317 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants traverse the rejection and note that claim 245 and 299 have been amended to recite that the nucleic acid component when introduced into a cell produces their respective product. Claim 265 has been amended to recite that the nucleic acid component in the claimed composition, which when present in a cell produces a non-natural nucleic acid product, which product comprises

(i) a nuclear localization sequence comprising a portion of snRNA, said snRNA comprising sequences for at least two stem loops present at the 3' end of native snRNA, and a reimportation signal and

(ii) a nucleic acid sequence of interest.

Applicants suggest that these amendments help to narrow the scope of the pending claims, and assert that the subject matter recited in the currently pending claims is adequately

described in the specification. Applicants argue that the specific phrases "primary nucleic acid construct", "a production center" "propagation", "production", and "inherent cell systems" are provided on pages 91-92, and indicate their belief that these phrases are fully supported and provide adequate description for claims reciting such phrases. Applicants also assert that the instant specification provides sufficient representative samples to support claims to the breadth of genus recited.

Regarding the use of terms such as a "primary nucleic acid construct", "a production center" "propagation", "production", and "inherent cell systems", these terms are considered to have open, non-limiting definitions in the specification due to the "for example" type language, and as such are read broadly. Claims incorporating these terms would need to be supported by a sample commensurate with such breadth. This is considered to comprise a vast number of species, as in the case of "inherent cell systems", or "production". As stated in the previous Office action, in order to be in possession of such breadth, applicant would need to disclose a representative number of species, the sum of which provides one of skill in the art with the knowledge to immediately envisage the genus. The claims containing the language above are extremely broad, encompassing virtually any living being capable of being infected by a virus, from bacteria to humans, and as such, the specification simply does not provide an adequate number of representative species to possess such breadth.

Applicants point to numerous examples of various embodiments of the claims, and assert that a representative number of species have been disclosed. For example, several examples of the primary nucleic acid constructs recited in claim 245 are provided, and four elements for propagation and production are recited: 1) single or multiple promoters, 2) self-priming

processes, 3) one or more primer binding sites and 4) multiple priming (pages 98-100). The following examples are also disclosed: 1) Example 21: A Primary Nucleic Acid Construct that Propagates Production Centers for the Production of Singles-stranded Antisense 2) Example 22: A Primary Nucleic Acid Construct that Propagates an RNA Production Center that is Reverse Transcribed to Create DNA Production Centers Capable of Directing Transcription 3) Example 23: A Primary Nucleic Acid Construct which Propagates a Double Hairpin Production Center for the Production of Single Stranded RNA 4) Example 24: A 'Nucleic Acid Construct which Propagates a Production Center capable of Inducible Cell Destruction 5) Example 25: Use of tRNA Primers to Create a Double-stranded DNA Production Center for Production of Single Stranded RNA. While it is agreed that applicants have disclosed species that fall within the breadth of their claim language, it is maintained that the terms "primary nucleic acid construct", "a production center" "propagation", "production", and "inherent cell systems" are so broad, that the claims read on virtually any living being capable of being infected by a virus. At issue is whether one would immediately envisage the genus claimed from the species disclosed. As indicated in the previous Office action, this bar is not considered to have been met for the reasons indicated above.

Applicants take issue with the assertion made in the Office Action that it is necessary to provide the chemical structure of the claimed nucleic acid constructs or components. At the outset, this is not believed to have been asserted in the previous Office action. If applicants disagree, applicants are requested to point out specifically where such a demand has been made. Again, at issue is whether the description provided by applicants would allow one of skill to envision the entire breadth of the claimed genus. The language recited in the claims are so broad

as to encompass not only the species disclosed by applicants, but also include virtually any living being that contains or makes RNA, such as a human, bacterium, or ribozyme as found in claim 245. This is a broad genus indeed. Applicants are not considered to have described an adequate number of species to envision the genus as claimed.

Applicants also argue that the specification discloses that the compositions of the present invention may be administered either *in vivo* or *ex vivo*. Applicants cite Yu et al., which discloses various methods for administering vectors into cells in culture as well as into whole organisms. Applicants also argue that methods for in vivo and ex vivo administration were well known in the art for expressing a nucleic acid product in a whole organism, and attach Exhibit C which contains references in support therein. These are not considered convincing, because applicants have not taught any nexus between structure and function in regards to the instantly claimed constructs that would allow for the practice of the claimed methods *in vivo*. In other words, applicants have not exemplified compounds that work *in vivo*, and moreover, have not taught what it is about *the structures described in the specification* would persuade one of skill that applicants where in possession of molecules that actually work *in vivo*.

5. Claims 263, 284, 286-290, 292, and 296-298 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of selectively expressing a nucleic acid product in a cell in cell culture (*in vitro*), does not reasonably provide enablement for methods of expressing the nucleic acids in a whole organism (*in vivo*). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants assert that methods were well known in the art for obtaining stable antisense and ribozyme molecule constructs and methods for their delivery into cells at the time of the priority date of the instant application, and provide Exhibit C as evidence. However, it is noted that not one of the articles presented actually shows *in vivo* inhibition. Because the instant rejection is based on the claims encompassing *in vivo* use, applicants submission of references which fail to describe any nucleic acid-mediated inhibition *in vivo* is not convincing evidence that the claimed nucleic acids will work *in vivo*.

Applicants have also submitted a number of references as exhibit D in support of the claims of enablement. However, all are at least 4 years, and most are at least 7 years past applicants' effective filing date of 1995. As per M.P.E.P. 2164.05(a), the "Specification Must Be Enabling as of the Filing Date". From the same section: "The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date."

Opalinska et al. supports the unpredictability of the art, by citing in the introduction: "Although conceptually elegant, the prospect of using nucleic-acid molecules for treating human malignancies and other diseases remains tantalizing but uncertain. The main source of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets." From the abstract of Stone et al., cited by the examiner in support of their claim of enablement: Antisense oligonucleotide-mediated knockdown has been used successfully as functional genomics tool in animal models of pain and analgesia yet skepticism regarding the

validity and utility of antisense technology remains. Contributing to this uncertainty is the lack of systematic studies exploring antisense oligonucleotide use *in vivo* and the many technical and methodological challenges intrinsic to the method."

While it is not disputed that infrequent success has been noted using antisense oligos *in vivo*, the question is whether such *in vivo* use has become predictable. Even applicants submitted references published up to7 years after filing indicate that methods pertaining to the *in vivo* use of oligonucleotides are unpredictable. It is maintained that even applicants' submitted references support the finding of unpredictability. Furthermore, none of the references speak to the snRNA targeting to the nucleus *in vivo*, which was set forth previously as a basis for unpredictability. For the same reasons as cited previously and discussed above, neither applicants' disclosure nor the prior art at the time of filing are considered to support the breadth of the claims insofar as they are drawn to *in vivo* practice.

Response to Claim Rejections - 35 USC § 102

6. Claims 265, 268, 270, 272-274, 278-280, 282-284 and 288-290, and 292 are rejected under 35 U.S.C. 102(e) as being anticipated by Sullenger et al. (U.S. Patent 5,854,038), for the same reasons of record as set forth in May 1, 2003.

Applicants respectfully traverse the rejection, and note that claim 265 has been amended to recite that the composition of the present invention comprises a nucleic acid component, which when present in a cell produces a non-natural nucleic acid product, which product comprises two elements: (i) a nuclear localization sequence comprising a portion of snRNA, said

snRNA comprising sequences for at least two stem loops present at the 3' end of native snRNA, and a reimportation signal. Applicants state that Sullenger et al. does not recite all of the elements of amended claim 265, because Sullenger et al does not disclose a nuclear localization signal containing a portion of an snRNA comprising sequences for at least two stem loops present at the 3' end of native snRNA, and a reimportation signal. Applicants point to the statement of Sullenger reciting the "localization to nuclear compartment utilizing antigen binding site found on most snRNAs."

This argument is not considered convincing, because Sullenger indeed discloses using snRNAs as localization tools, as evidenced from the above passage, and since furthermore, the limitation reciting two 3' stem loop structures on the snRNA is an inherent structural feature of U1 snRNA, as evidenced in figure 41 of the instant application, and the passage from applicants specification of page 43: "Entities which specify cellular location include:... nucleic acid species such as the snRNAs U1 and U2 which associate with cyloplasmic proteins and localize in the nucleus (Zieve and Sautereauj 1990 Biochemistry and Molecular Biology 25;1, incorporated by reference)." Therefore, since the limitations newly recited in the claims are considered inherent to snRNA's, and because Sullenger clearly contemplated using snRNAs as localization tools, this recitation does not free the claims from the prior art.

7. Claims 245, 249, 250 are rejected under 35 U.S.C. 102(e) as being anticipated by Hinuma et al. (U.S. Patent 6,538,107), for the same reasons of record as set forth in the Office action mailed May 1, 2003.

Applicants point out that claim 245 has been amended to recite that the primary construct when introduced into a cell produces a secondary nucleic acid component which produces a nucleic acid product, or a tertiary nucleic acid component, or both. Applicants assert that the antisense construct of Hinuma does not actually produce a nucleic acid product or tertiary nucleic acid product. However, this is not convincing, because a broad reasonable interpretation is claim 245 is still taught by Hinuma et al. For example, claim 245 when given its broadest reasonable interpretation, provides for the same teachings as taught by Hinuma et al. For example, claim 245 claims a composition comprising a primary nucleic acid component which upon introduction into a cell produces a secondary nucleic acid product which produces a nucleic acid product. This reads on any antisense oligo such as those taught by Hinuma et al., because an antisense oligo as taught by Hinuma et al. could be primary nucleic acid product when introduced into a cell hybridizes to its target to produce a secondary nucleic acid product (i.e. the hybridized, double stranded nucleic acid) which is then cleaved by RNase H (as known to those of ordinary skill) to produce a nucleic acid product, i.e. the cleaved nucleic acid. Therefore, the newly added claim limitations still cause the claim to read on the prior art, and thus remains rejected.

Response to Claim Rejections - 35 USC § 103

8. Claims 245, 256, 257, 265, 317, 273 and 274 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sullenger et al. (U.S. Patent 5,854,038) in view of ter Meulen et al. (U.S. Patent 5,646,032), for the same reasons of record as set forth in the Office action mailed

May 1, 2003. Since DeYoung is no longer being applied under 35 U.S.C. § 102(b), it is no longer applicable here, and arguments pertaining thereto will not be addressed.

Applicants traverse the rejection, on the grounds that the composition of claims 245, 256, 257, 265, 317, 273 and 274 can be distinguished from Sullenger. Applicants assert that Sullenger does not disclose or suggest a composition comprising a primary nucleic acid component which upon introduction into a eukaryotic cell produces a secondary nucleic acid component which produces a nucleic acid product, or a tertiary nucleic acid component, or both, in said eukaryotic cell.

However, this is not convincing, because Sullenger indeed discloses using snRNAs as localization tools, as evidenced from the passage stating that it is useful to incorporate "localization to nuclear compartment utilizing antigen binding site found on most snRNAs into their constructs. As pointed out above, the limitation reciting two 3' stem loop structures on the snRNA is an inherent structural feature of U1 snRNA, as evidenced in figure 41 of the instant application, and applicants disclosure stating that "Entities which specify cellular location include:... nucleic acid species such as the snRNAs U1 and U2 which associate with cyloplasmic proteins and localize in the nucleus (Zieve and Sautereauj 1990 Biochemistry and Molecular Biology 25;1, incorporated by reference)." This demonstrates that snRNA is a localization tool, and would thus cause reimportation. Since it inherently has two 3' stem loop structures, the limitations newly recited in the claims does not free the claims from the Sullenger as applied herein.

Although applicants assert that the secondary reference, ter Meulen, would' not add anything of significance, this is not considered to be convincing. Sullenger teaches antisense or

decoy RNA and/or DNA molecules, similar to the the decoys taught by ter Muelen et al. directed against a viral replication targets. Since Sullenger taught the design of decoys generally to any viral target, and as ter Muelen et al. taught, the viral replication protein is an essential molecule for the replication of the virus, one of ordinary skill would have been motivated to target this sequence with a decoy to achieve saturation binding of the promotor and lower the rate of viral replication in the infected cell. Thus, contrary to applicants contentions, one of ordinary skill in the art would have been motivated to combine the teachings of the references, and thus, the invention is considered *prima facie* obvious in the lack of evidence to the contrary.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James Douglas Schultz, PhD